

08-16-06

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Adriano Aguzzi *et al.*

Serial No.: 09/554,567

Filed: September 1, 2000

For: Diagnostics and Therapeutics for
Transmissible Spongiform Encephalopathy and
Methods for the Manufacture of Non-Infective Blood
Products and Tissue Derived Products

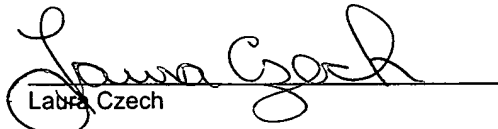
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Examiner: Ulrike Winkler, Ph.D.

Group Art Unit: 1648

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Laura Czech

APPEAL BRIEF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is being submitted pursuant to 37 CFR §41.37. A Notice of Appeal was timely filed on January 20, 2006. Pursuant to 37 CFR §41.20(b)(2), a check in the amount of \$500.00 is enclosed for the filing of this Appeal Brief. In addition, a Petition for a five-month extension of time for filing this Appeal Brief accompanies this paper along with a check in the amount of \$2160.00. If any additional fees are required as a result of the filing of this paper, the Commissioner is hereby authorized to charge Deposit Account No. 23-0785 for any such fees.

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Real Party in Interest

The University of Zurich is the real party in interest in this appeal.¹

Related Appeals and Interferences

There are no related appeals, interferences or judicial proceedings known to Appellant, Appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

Status of Claims

Claims 1-34 and 38-40 have been canceled. Claims 35-37 are rejected and are the subject of this appeal.

Status of Amendments

There have been no amendments made to the claims or specification subsequent to the mailing of the final Office Action on September 21, 2005.

Summary of Claimed Subject Matter

¹ The assignment recorded on September 11, 2000 at reel/frame 011156/0452 contains an error. The recordation sheet says that the assignment was made from the inventors to Abbott Laboratories, Inc. However, the actual assignment is to the University of Zurich.

The present invention relates to Transmissible Spongiform Encephalopathy (hereinafter "TSE"). TSE comprises a group of slow degenerative diseases of the central nervous system, such as Creutzfeld-Jakob disease (hereinafter "CJD") in man or Bovine Spongiform Encephalopathy (hereinafter "BSE") in cattle, which is also known as "mad cow disease". Specifically, the present invention relates to methods of identifying TSE-infected B-cells and T-cells in a test sample.

It is believed that TSE is caused by the pathogenic agent known as a "prion." It is known in the art that prions are devoid of nucleic acid and are identical with PrP^{Sc} , which are the disease or modified forms of the normal host protein, PrP^{C} (See, the specification, page 2, lines 23-27). PrP^{Sc} is a protease-resistant form of PrP^{C} . So far, no chemical differences have been detected between PrP^{Sc} and PrP^{C} .

As mentioned briefly above, the present invention is directed to methods of identifying TSE-infected B-cells and T-cells. Applicants were the first to determine the roles of different components of the immune system by using a panel of immune-deficient mice inoculated with prions. Specifically, Applicants have discovered that differentiated B-cells are crucial for neuroinvasion by TSE while T-cells play a secondary role in TSE infectivity. Based on these findings, assays according to the present invention are provided which contemplate the monitoring of biological or biochemical parameters of B-cells and/or T-cells to determine the occurrence of TSE infection. The invention takes advantage of the fact that, as opposed to PrP^{C} , PrP^{Sc} is resistant to proteinase K digestion. Because of this fact, any form of PrP^{C} remaining in

the B-cells and/or T-cells after digestion with proteinase K will necessarily be PrP^{Sc}. Therefore, if the cells are exposed to anti-PrP^C antibodies, the antibodies will recognize only abnormal PrP^{Sc} proteins, thus indicating TSE.

Three independent claims are involved in this Appeal, namely, claims 35, 36, and 37. Each of these claims recites virtually identical steps of identifying TSE-infected cells. The difference between the claims is that claim 35 is directed to the identification of TSE-infected B-cells, claim 36 is directed to the identification of TSE-infected T-cells, and claim 37 is directed to the identification of TSE-infected B-cells and T-cells.

More specifically, the claimed methods comprise the steps of:

- obtaining a test sample suspected of TSE infection;
 - collecting B-cells and/or T-cells from the test sample;
 - subjecting said B-cells and/or T-cells to homogenization;
 - subjecting said homogenized B-cells and/or T-cells to proteinase K digestion;
 - subjecting said digested B-cells and/or T-cells to SDS Page immunoaffinity chromatography blots;
 - contacting said blots with an anti-PrP antibody,
- wherein in the presence of a signal from the anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells and/or T-cells;
- identifying TSE-infected B-cells and/or T-cells based on the presence of said signal; and

-wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection (claim 35), the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection (claim 36), or the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection and the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection (claim 37).

Support for the resistance of PrP^{Sc} to proteinase K digestion is found in the specification beginning on page 12 last paragraph through page 13, line 3. Figure 10 further illustrates that PrP^{Sc} levels can be detected in infected T-cells and B-cells in a Western blot after proteinase K digestion.

Grounds of Rejection to be Reviewed on Appeal

There is only one outstanding ground of rejection that is the subject of this Appeal. Specifically, claims 35-37 are rejected under 35 U.S.C. §103(a) as being unpatentable over O'Rourke et al., (U.S. Patent No. 6,165,784) (hereinafter "O'Rourke") and/or Korth et al., (*Nature*, 390: 74-77 (November 6, 1997)) (hereinafter "Korth"), in view of Kuroda et al., (*Infection and Immunity*, 41:154-61 (1983)) (hereinafter "Kuroda") and/or Manuelidis et al., (*Science*, 200: 1069-1071 (1978)) (hereinafter "Manuelidis").

Argument

The Examiner rejected all of the pending claims as being unpatentable over the combination of the teachings of O'Rourke and/or Korth in view of Kuroda and/or Manuelidis.

According to the Examiner, Kuroda teaches that both B-cells and T-cells can transmit TSE, and Manuelidis teaches the importance of focusing on these cellular populations to increase the sensitivity of assays for TSE infectivity. The Examiner further maintains that both O'Rourke and Korth disclose using antibodies as a method of detecting the disease-causing agent. The Examiner alleges that it would have been obvious to apply the techniques taught by O'Rourke and/or Korth to the infected tissue disclosed by Kuroda and/or Manuelidis in order to improve the sensitivity of the TSE tests by collecting samples containing B-cells and/or T-cells. The Examiner finds the motivation to combine these references in avoiding having to utilize live animals to test for infectivity in the B-cells and/or T-cells.

The Examiner's rejection is erroneous for the following reasons: 1) neither Kuroda nor Manuelidis explicitly teach that B-cells and/or T-cells can transmit TSE; 2) there is no motivation to combine these references; and 3) the Korth reference teaches away from the Applicants' invention.

A. Neither Kuroda nor Manuelidis teach that B-cells and/or T-cells can transmit TSE

Throughout the prosecution of this application, the Examiner has maintained that Kuroda teaches that both B-cells and T-cells can transmit TSE and that Manuelidis teaches that it is important to focus on these cellular populations to increase the sensitivity of assays for TSE infectivity. These statements are overly broad and not entirely correct.

Kuroda reported the results of a study in BALB/c mice that he thought were infected with a Japanese strain of a CJD (a variant of TSE) **virus**. Kuroda detected the “virus” in the brain, spleen, lung, thymus, liver, kidney and blood (but not the urine) of the infected mice at various periods in time after inoculation. Of the examined tissues, the highest infectivity was found in the brain and spleen. Kuroda examined the spleen cells to determine what types of cells were actually infected with the virus. Initially, he found that spleen macrophages, T-cells, and B-cells were infected. Of these cells, the highest concentration of the virus was found in the lymphocyte fraction. When Kuroda examined the infectivity of various subpopulations of lymphocytes from these “virus”-infected mice, he found that large lymphocytes or blastoid cells in the lower-density fractions from the spleen exhibited the most infectivity.

Accordingly, Kuroda mistakenly believed that CJD was caused by a virus. The very point of the study was to “obtain data on the mode of replication and temporal distribution of CJD virus in relation to onset of the disease and to determine the important implication of the hematogeneous route of virus dissemination” (See, Kuroda, page 154, 1st and 2nd paragraphs). It was later determined that TSE is the result of an

abnormal prion, not a virus. Nowhere does Kuroda disclose or suggest that B-cells and/or T-cells transmit TSE.

Second, like Kuroda, Manuelidis also mistakenly believed that CJD was caused by a virus (See, Manuelidis, page 1069, Abstract). In a study using guinea pigs, Manuelidis “demonstrated” that “there is a viremia in experimental [CJD].” Manuelidis isolated the buffy coat (which contained white blood cells) from CJD-infected guinea pigs, injected the buffy coat into disease free guinea pigs, and observed the animals for the progression of the disease. Manuelidis theorized that maximal infectivity should reside in the buffy coat rather than in the serum or red blood cells. While it may be true that Manuelidis established that the disease-causing agent is present in the buffy coat of the blood, this information is of a generic kind when compared with the specificity of the present invention (specifically, methods of identifying TSE-infected B-cells and T-cells in a test sample by collecting the cell types and directly testing them for the presence of prion associated with the TSE). In fact, Manuelidis does not discuss at all the role played by the B-cells and T-cells in transmission of the TSE.

Having recognized that Kuroda and Manuelidis incorrectly taught that the disease-causing agent was a virus, instead of a prion, the Examiner dismissed the importance of this crucial difference by arguing that when the references were published, the prion protein theory of disease was not generally accepted. However, Appellants respectfully submit that it is immaterial for an obviousness rejection whether or not a correct theory of the disease was generally accepted at the time a reference is

published. Rather, what is material is whether the reference by itself or in combination with other references renders the invention obvious to a person of ordinary skill in the art (hereinafter referred to as a “skilled artisan”). Applicants contend that given that Kuroda and Manuelidis were fundamentally wrong about the nature of the disease-causing agent and were not even aware of the existence of prions, the references simply cannot render obvious the method involving the steps of collecting B-cells and/or T-cells from a test sample and directly testing these cell types for the presence of prions associated with TSE.

According to the Examiner, “even if the references erroneously referred to the disease-causing agent as a virus this (sic) does not detract from the important observation made in the references” (See, Office Action mailed on September 21, 2005, page 4). The “important observation” is presumably that CJD is associated with lymphocyte cells. While it is true that the references disclosed that the highest concentration of the “virus” was in lymphocyte cells, it is unclear how this makes it obvious to test specifically B-cells and T-cells for the presence of prion associated with TSE. The Examiner argues that it would have been obvious at the time the invention was made to improve the sensitivity of antibody-based assays by collecting samples containing B-cells and/or T-cells and testing for the presence of TSE using an antibody-based system. However, the Examiner cannot have it both ways. On the one hand, the Examiner claims that a skilled artisan would disregard the scientific conclusion of Kuroda and Manuelidis that CJD is a virus-based infection. On the other hand, the Examiner claims that the same skilled artisan would accept Kuroda and Manuelidis’

conclusions that lymphocyte cells are associated with CJD. The Examiner offers no scientific rationale as to why a skilled artisan would disregard one finding of the references while embracing the another. Applicants submit that it is more likely that a skilled artisan would either agree with Kuroda and Manuelidis that CJD is a viral infection (and in that case, would not be motivated to test for abnormal prions) or disregard the references completely (and in that case, would not be motivated to concentrate lymphocyte cells).

Therefore, Applicants respectively submit that the claimed invention is not *prima facie* obvious to a skilled artisan.

B. There Is No Motivation to Combine the References

The Federal Circuit has repeatedly held that three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not be based on applicant's disclosure. *Manuel of Patent Examining Procedure* §2142 (8th Edition, October 2005 Revision) citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also, *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

In the present application, the Examiner has failed to convincingly demonstrate either a suggestion or motivation to combine the asserted references. The Examiner merely combined the disclosures of Kuroda and Manuelidis demonstrating that B-cells and T-cells (among other lymphocytes) may contain the TSE-causing agent with the disclosures of O'Rourke and Korth's of antibody-based methods of detecting TSEs and asserted that such combination would increase the sensitivity of detection assays. As discussed above, Kuroda and Manuelidis mistakenly identified a virus as a TSE-causing agent and indicated that injection of lymphocytes into healthy animals leads to the TSE infection. Neither Kuroda nor Manuelidis taught or suggested that prions played a crucial role in the transmission of TSEs. Korth taught a monoclonal antibody specific for PrP^{Sc} in brain homogenates and O'Rourke taught antibody-based methods to detect PrP^{Sc} as an indication of TSEs.

More specifically, O'Rourke described detection of PrP^{Sc} using antibodies that bind to PrP^{Sc}. While O'Rourke focused on third eyelid lymphoid tissues in ruminant animals, nowhere did O'Rourke disclose or suggest the specific role played by B-cells in transmission of TSEs.

The Examiner's rationale is as follows:

Both O'Rourke et al. and Korth et al. teach methods of detecting the disease form of prion protein after proteinase K digestion followed by SDS-page electrophoresis and blotting onto a membrane. One of ordinary skill in the art would have a high expectation of success in applying the techniques taught by O'Rourke et al. or Korth et al. to the infected tissue disclosed by Kuroda et al. or Manuelidis et al. It would have been obvious at the time the invention was made

to improve the sensitivity of the TSE tests by collecting samples containing B cells and/or T cells and testing for the presence of TSE using an antibody based system. The ordinary artisan at the time the invention was made would have been motivated to this (sic) in order to avoid having to utilize animals in order to test for infectivity in the B and/or T cell population. The ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with antibodies. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references (Office Action mailed on November 14, 2003, pages 6-7).

It appears that the Examiner's rationale for combining the references is that a skilled artisan would have been motivated to do so to avoid having to utilize live animals to test for TSE infectivity. According to the Examiner, the skilled artisan would have concluded that B-cells and T-cells are known to be infected with the TSE-causing agent and would have been motivated to concentrate these cell types to increase the sensitivity of detection assays.

However, this reasoning is flawed. According to the Federal Circuit, the motivation or suggestion to combine the references must be found either in the references themselves, in the knowledge generally available to one of ordinary skill in the art, or from the nature of the problem to be solved, leading the inventors to look to the references for possible solutions to that problem. *Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686, 1691 (Fed. Cir. 2004). Both the suggestion and the reasonable

expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Moreover, the showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence. *Teleflex Inc. v. Ficosa North America Corp.*, 63 USPQ2d 1374, 1387 (Fed. Cir. 2002).

It is beyond dispute that neither Kuroda nor Manuelidis contain any hints or suggestions to combine their teachings with an antibody-based methods to detect abnormal prions associated with TSEs. Indeed, it would be impossible for either Kuroda or Manuelidis to contain such hints or suggestions given that both of these references mistakenly believed that TSEs were caused by a virus. The knowledge generally available to a skilled artisan also does not contain any motivation or suggestion to combine the references. By 1997 (the priority date of the instant application), the majority of scientific literature would have led a skilled artisan to heavily discount the disclosures of Kuroda and Manuelidis since by then the emerging scientific consensus was that the infective agent of TSE was not a virus. In fact, both O'Rourke and Korth identify prions, not viruses, as TSE-causing agents. Why would a skilled artisan be motivated to combine the references which identify different disease-causing agents? Finally, the nature of the problem to be solved would not lead a skilled artisan to combine the references. The problem to be solved was to develop a reliable method of identifying and/or monitoring TSE in infected organisms or in organisms suspected of being infected. There was no motivation to combine the references which taught that

TSE was caused by a virus with references which taught the antibodies to abnormal prions and antibody-based methods to detect abnormal prions.

It is true that the recognition that some advantage or expected beneficial result would have been produced by combining references provides the strongest rationale for their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). However, in the instant application, a skilled artisan would not have expected any advantage or beneficial result from the combination of the references since a skilled artisan who believed in the prion nature of TSE disease would have discounted the findings of researchers who believed that TSEs were caused by a virus.

The Federal Circuit has consistently cautioned Examiners against succumbing to a hindsight-based analysis. “Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). “Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight.” *Id.*

Of course, in hindsight it is “obvious” to combine the disclosures of Kuroda, Manuelidis, Korth, and O’Rourke to develop a reliable test for TSEs. However, it is “obvious” only after Applicants’ careful and meticulous investigation of the role that B-

cells play in transmission of TSEs. Prior to the Applicants' invention, the roles of different components of the immune system, and in particular, the primary role of B-cells in transmission of TSEs were not known. Applicants were the first to identify B-cells and B-cells dependent processes as a limiting factor in the development of TSE after peripheral infection (See, Specification, page 27, first paragraph). Even if one assumes that Kuroda and Manuelidis determined that lymphocytes were involved in transmission of TSEs, neither Kuroda nor Manuelidis have identified B-cells as the specific subset of the lymphoreticular system (hereinafter "LRS") responsible for disease spread. Without this knowledge, it cannot be said that it was obvious to detect the presence of TSE-infected B-cells and/or T-cells by contacting the proteinase K-digested cells with an anti-PrP antibody.

Accordingly, there is no motivation or suggestion to combine the references.

C. Korth Reference Teaches Away From Applicants' Invention

A fair reading of the Korth reference would likely teach away from Applicants' invention. A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994).

While the Examiner claims that the Korth reference supports his determination of obviousness, "it is impermissible within the framework of 35 U.S.C. §103 to pick and

choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.” *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). Korth claimed to have identified the antibody, 15B3, specific for an abnormal prion, PrP^{Sc}. This antibody specifically precipitates bovine, murine or human PrP^{Sc}, but not PrP^C (See, Korth, page 74). According to Korth, “the identification of an antibody that binds selectively to PrP^{Sc} from various species provides a new means to identify PrP^{Sc} directly **without using proteinase K digestion as a criterion**” (emphasis by Applicants) (See, Korth, page 77). In other words, Korth suggests that a skilled artisan would be able to avoid the step of proteinase K digestion and to precipitate PrP^{Sc} directly. However, Applicants’ claims specifically recite a step of subjecting B-cells and/or T-cells to proteinase K digestion (See, claims 35-37). It is not surprising since Applicants’ method involves using an antibody which is not specific for PrP^{Sc} and therefore, requires a step of proteinase K digestion to allow the antibody to preferentially bind to proteinase K-resistant PrP^{Sc}.

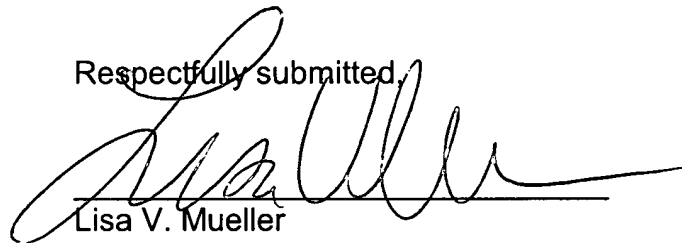
Therefore, a fair reading of the Korth reference would not have led a skilled artisan to Applicants invention and, in fact, would have led a skilled artisan in a different direction.

CONCLUSION

In conclusion, the none of the cited references render the claimed invention obvious. Neither Kuroda nor Manuelidis teach that B-cells and/or T-cells can transmit TSE. While the references teach that lymphocyte fractions (Kuroda) and buffy coat

(Manuelidis) may play a role in TSE, neither of these references focused specifically on B-cells and/or T-cells. Moreover, both Kuroda and Manuelidis mistakenly believed that CJD was caused by a virus and were not even aware of the existence of prions, the true pathogenic agents causing TSE. O'Rourke and Korth do not cure these deficiencies since neither O'Rourke nor Korth disclose or suggest the specific role played by B-cells and/or T-cells in transmission of TSEs. Furthermore, there is no motivation or suggestion to combine these references to arrive at a reliable test for TSE, such as the test claimed in the instant invention. Accordingly, Applicants respectfully submit that the rejection of claims 35-37 under 35 U.S.C. §103 (a) as being unpatentable over O'Rourke, and/or Korth in view of Kuroda and/or Manuelidis is in error and should be reversed.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Lisa V. Mueller', written over a horizontal line.

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Claims Appendix

35. A method of identifying TSE-infected B-cells associated with transmissible spongiform encephalopathy in a test sample, the method comprising the steps of:
obtaining a test sample suspected of TSE infection;
collecting B-cells from the test sample;
subjecting said B-cells to homogenization;
subjecting said homogenized B-cells to proteinase K digestion;
subjecting said digested B-cells to SDS Page immunoaffinity chromatography

blots;

contacting said blots with an anti-PrP antibody,
wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells;
identifying TSE-infected B-cells based on the presence of said signal; and
wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection.

36. A method of identifying TSE-infected T-cells associated with transmissible spongiform encephalopathy in a test sample, the method comprising the steps of:

obtaining a test sample suspected of TSE infection;
collecting T-cells from the test sample;
subjecting said T-cells to homogenization;
subjecting said homogenized T-cells to proteinase K digestion;
subjecting said digested T-cells to SDS Page immunoaffinity chromatography

blots;

contacting said blots with an anti-PrP antibody,
wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected T-cells;
identifying TSE-infected T-cells based on the presence of said signal; and
wherein the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection.

37. A method of identifying TSE-infected B-cells and TSE-infected T-cells associated with transmissible spongiform encephalopathy in a test sample, the method comprising the steps of:

obtaining a test sample suspected of TSE infection;
collecting B-cells and T-cells from the test sample;
subjecting said B-cells and T-cells to homogenization;
subjecting said homogenized B-cells and T-cells to proteinase K digestion;
subjecting said digested B-cells and T-cells to SDS Page immunoaffinity chromatography blots;
contacting said blots with an anti-PrP antibody,
wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells and TSE-infected T-cells;

identifying TSE-infected B-cells and TSE-infected T-cells based on the presence of said signal; and
wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection and the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection.

Evidence Appendix

Copies of cited references are enclosed.

Related Proceedings Appendix

Not Applicable.